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"UNNATURAL ALKALOIDS"

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Abstract - There are many good reasons for synthesizing and studying "unnatural" relatives of biologically active natural products, particularly alkaloids. Such "unnatural" substances may include optical isomers, deoxy-congeners, dimers and metabolites from mammalian and human tissue, related, but not identical, to plant alkaloids. The chemistry and biological behavior of such "unnatural" alkaloids is presented.

INTRODUCTION (see Note a)

Most alkaloids isolated from plant materials are optically active and rarely encountered as racemates. Alkaloids used in medicine are usually pure enantiomers. It has often been demonstrated that biological activity is manifested by only one of the two enantiomers, frequently prepared by total synthesis of its racemate followed by optical resolution. The finding that unnatural (+)-dihydroquinine and natural (-)-dihydroquinine are equally effective as antimalarial agents (Ref. 1) suggests, that a thorough biological evaluation of interesting alkaloids should include the study of all possible stereoisomers, including optical antipodes. Alkaloids containing aromatic moieties are frequently substituted with a variety of oxygen functions on the aromatic ring. The synthesis of analogs lacking these could afford a variety of potentially interesting "unnatural" products, especially if such a functionality could be regenerated by a biochemical process *in vivo*. Natural products of a more complex nature, such as dimeric alkaloids, are often poorly characterized and sometimes have varied physical data reported for them from various laboratories. An unambiguous synthesis of their enantiomers, starting from optically pure materials belonging to the antipodal series, could help to clarify these differences.

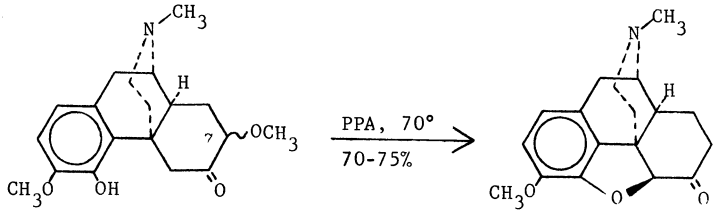
Finally, there is, a growing interest in alkaloidal compounds originating from sources other than plants. Some substances isolated from mammalian tissue (Ref. 2) and originating from L-dopa, an established alkaloids precursor, may be disease related and their presence could be of diagnostic value. One wonders how humans and animals biosynthesize such "un-natural" alkaloids which differ so little from their relatives from the plant kingdom.

It is mainly for these reasons that our laboratory embarked on a detailed study of "unnatural" alkaloids, and the results achieved over the past three years are summarized.

UNNATURAL ALKALOIDS OF THE (+)-MORPHINE SERIES

The preparation of substantial quantities of (+)-morphine and several of its congeners from natural (-)-sinomenine was facilitated by a greatly improved yield in the cyclization of (+)-dihydrosinomenine (1) to (+)-dihydrocodeinone (2), as shown in Fig. 1 (Ref. 3).

Fig. 1

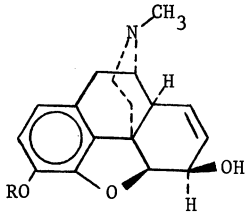


(1) (2)

Note a: Details of our own studies will be published elsewhere.

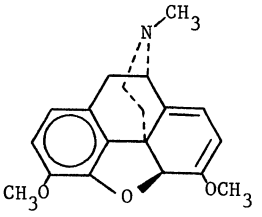
Biological evaluation of the "unnatural" opium alkaloids shown in Fig. 2 (Refs. 3 & 4, see Note b) established that they are practically devoid of analgesic activity (Refs. 5 & 6) and do not bind to the opiate receptor (Ref. 6). They, show however CNS-effects similar to those produced by natural morphine when injected into certain brain areas of rats (Ref. 6).

Fig. 2



(+)-Morphine, R = H

(+)-Codeine, R = CH_3



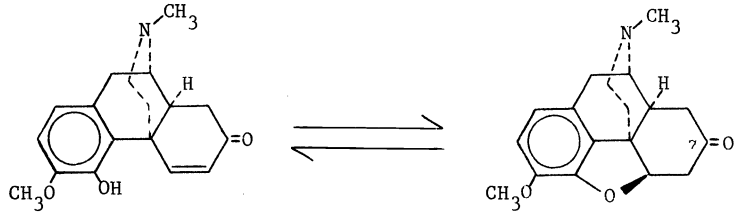
(+)-Thebaine

These observations suggest that there are at least two classes of receptors, one stereospecific and blocked by narcotic antagonists such as naloxone, and the other unspecific and not blocked by narcotic antagonists. Precipitated abstinence may be due, in part, to a selective blockade of receptors of the first class but not of those of the second. A more detailed study of (+)-codeine, which has given erratic results in analgesic screening with mice, as well as its evaluation as a potential antitussive agent, has been undertaken.

BY-PRODUCTS FROM THE ACID CATALYZED CYCLIZATION OF DIHYDROSINOMENINE

During our studies of "unnnatural" compounds of the (+)-morphine series, we obtained at different stages various by-products. The most interesting one is an isomer of (+)-dihydrocodeinone (2), obtained repeatedly in 10-15% yield in the PPA catalyzed cyclization step (Fig. 1). There is good spectral evidence (nmr, ir) that this isomer, which shows a single spot on tlc, is in solution a 1:1 mixture of the unsaturated 7-oxomorphinan (3) and its oxygen bridged 7-oxodihydromorphine derivative (4) (Fig. 3). This equilibrium is the result of a Michael addition and its reversal.

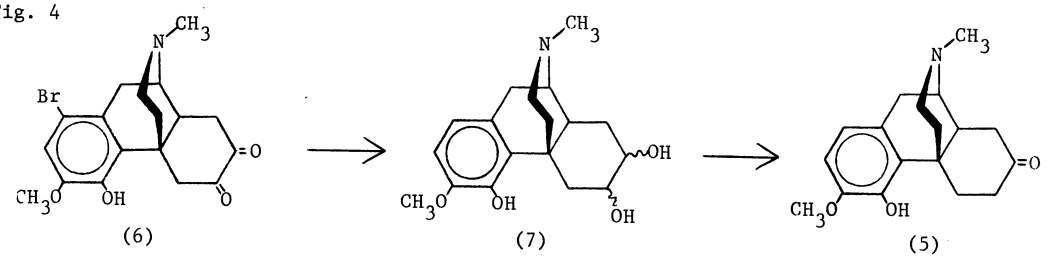
Fig. 3



(3) (4)

Chemical evidence for the presence of the unsaturated ketone (3) was obtained by O-acetylation and catalytic hydrogenation, affording the acetoxy derivative of (3) as an oil and the crystalline saturated (+)-ketone (5), respectively. The former can be hydrolyzed to the original (3+4) mixture and the latter seems to be identical to the product obtained by Goto et al. and named (+)-epidihydrothebainone (Ref. 7). Its optical isomer (5) was prepared from the known (-)-bromodiketone (6) of the natural morphine series (Ref. 8) by conversion to the desbromodiol (7) and dehydration with sulfuric acid as illustrated in Fig. 4. This ketone is not identical with (-)-dihydrothebainone.

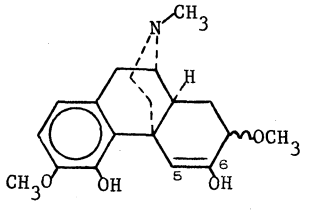
Fig. 4



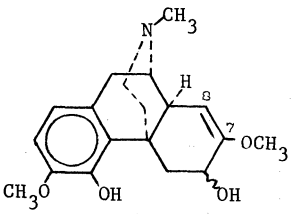
(6) (7) (5)

Note b: Without generous supplies of natural (-)-sinomenine from the Tanabe Research Laboratory (Dr. M. Takeda), the Shionogi Research Laboratory (Dr. W. Nagata) and by Prof. I. Yamamoto, of Tokyo's University of Agriculture, the work relating to (+)-morphine could not have been accomplished.

Fig. 5



(8)



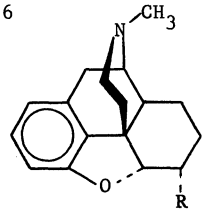
(9)

The cyclization of (1) with PPA affording (2) and the isomeric ketone mixture (3 + 4) can be rationalized by the formation of two different enol intermediates. The 5,6-enol (8) explains the cyclization to dihydrocodeinone (2), whereas the allylic alcohol (9), with the enol double bond shifted to the 7,8-position, would account for the formation of the unsaturated ketone (3). The fact that keto-alcohols (7-OH instead of 7-OMe in 1) do not afford 7-keto compounds by treatment with PPA suggests, that the formation of the oxygen bridge in the cyclization reaction may be preceded by cleavage of the C-7 methoxy group.

3-DEOXYMORPHINES AND CONGENERS

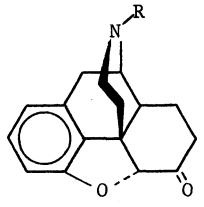
The assumption that the phenolic group in natural morphine is essential for analgesic activity (Ref. 9) has never been tested. Removal of a phenolic hydroxy group by catalytic hydrogenolysis of its N-phenyltetrazolyl ether succeeds well with dihydromorphine, as in other series of natural products (Ref. 10). The product 3-deoxydihydromorphine (10), is a convenient starting material for the preparation of analogs, including 3,6-dideoxydihydromorphine (11) (Fig. 6).

Fig. 6



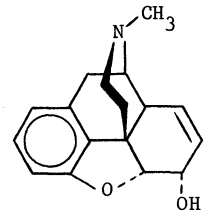
(10), R = OH

(11), R = H



(12), R = CH_3

(13), R = CO_2Et



(14)

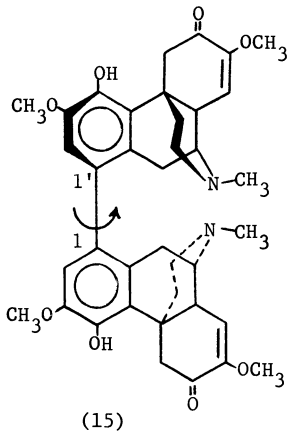
Compound (11) representing the basic five membered skeleton of dihydromorphine is particularly interesting. The synthesis of 3-deoxymorphine (14) was accomplished by the procedure used for the synthesis of (+)-codeine (Ref. 11). This required the preparation of the ketone (12) and its conversion into the carbamate (13). Alkylation with phenylselenenyl chloride, oxidative elimination and reduction with lithium aluminum hydride gave 14. The 3-deoxymorphine derivatives (10), (11) and (14) exhibit analgesics properties in experimental animals, retaining 50-70% of the activity of the parent dihydromorphines, but having a 20-30% weaker binding capacity to the opiate receptor. The consequence of weaker binding of opioid derived analgesics to the opiate receptor will be studied to ascertain whether 3-deoxymorphine and its dihydro analogs constitute a new type of analgesic agents. The deoxydihydromorphine (10) has recently been converted into dihydromorphine by a strain of Streptomyces argenteolus (see Note c). If microbial hydroxylation of compounds such as (10) should prove practical, this might be of considerable importance in connection with a total synthesis of natural morphine.

DIMERS OF NATURAL AND UNNATURAL SINOMENINE

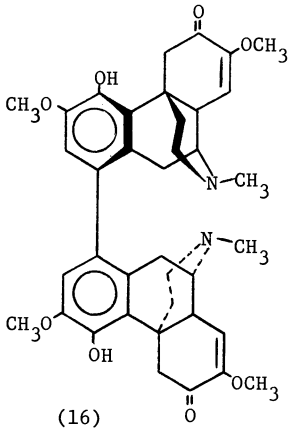
Oxidation of natural (-)-sinomenine (1) with chemical oxidizing agents affords a mixture of two dimers named (+)-disinomenine and (+)-ψ-disinomenine (Ref. 5). Chemical data corroborated by Goto et al. (Ref. 5) suggests that both are isomers with restricted rotation around their 1,1'-biphenyl axis. It has not been established whether structure 15, with the ethano bridge from the lower moiety above the corresponding unit of the upper moiety represents (+)-disinomenine or its ψ-dimer (Fig. 7.).

Note c: Experiments carried out by Prof. D. Perlman, School of Pharmacy, University of Wisconsin, Madison, Wisconsin, USA.

Fig. 7



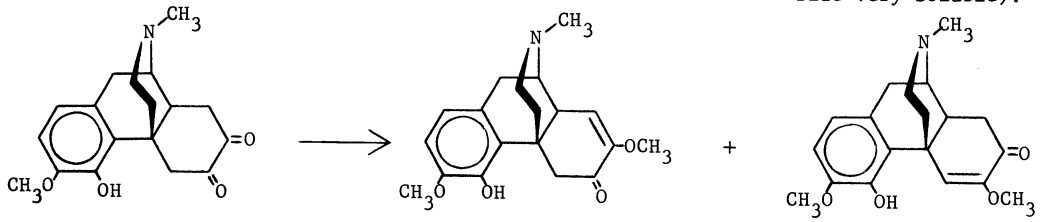
(15)



(16)

Clarification regarding this point is complicated by the fact that the physical data reported for (+)-ψ-disinomenine differs considerably from our own findings. The ψ-isomer can be readily separated by preparative tlc on silica gel and may be prepared in quantity since both isomers can be thermally equilibrated at 235° to a 1:1 mixture. To determine whether the dimers of the natural (+)-series (15 and 16) are optically pure, their antipodes were synthesized from "unnatural" sinomenine (18), as shown in Fig. 8. The known (-)-diketone (17) (Ref. 12) was O-methylated as described in the (+)-series (Ref. 13) and the two isomers (18) and (19) separated by chromatography. Unnatural (+)-sinomenine (18), upon oxidation with aqueous silver nitrate, afforded the two (-)-dimers corresponding, with the exception of their opposite optical rotations, in all respects to the (+)-enantiomers. The marked differences in the water solubility of the dihydrochlorides of these dimers can be utilized for their further characterization (disinomenine dihydrochloride almost insoluble, ψ-disinomenine dihydrochloride very soluble).

Fig. 8



(17) (18) (19)

The physical data obtained for the four disinomenine isomers are listed in Fig. 9. All dimers tend to crystallize with solvents of crystallization which can only be removed with a loss of the crystal's integrity, a fact which has prevented successful single x-ray analysis.

CHARACTERISTIC DATA OF OPTICALLY PURE DISINOMENINES

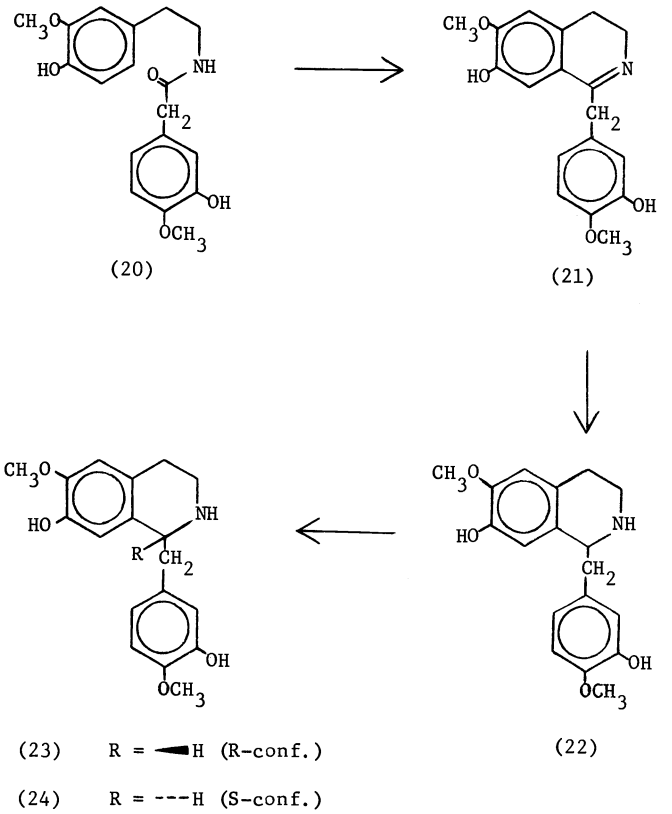
Compound (MeOH)	M.P., corr.	$[\alpha]_D^{20}$, $CHCl_3$
(+)-Disinomenine	221-223°	+ 86°
(-)-Disinomenine	221-223°	- 88°
(+)-ψ-Disinomenine	209-210°	+ 51°
(-)-ψ-Disinomenine	205-207°	- 52°

Fig. 9

N-NORRETICULINE, RETICULINE, TETRAHYDROPAPAVEROLINE AND ISOPAVINANES

Optically active N-norreticuline is a key intermediate in the biosynthesis of plant benzylisoquinoline alkaloids (Refs. 14 & 15). The synthesis of racemic N-norreticuline (22) can now be accomplished in high yield by the sequences shown in Fig. 10. The readily available amide (20) is cyclized without protection to dehydronorreticuline (21), and in variation of the original procedure (Ref. 16), reduced in situ to (22), isolated as its tosylate salt. Optical resolution of (22) in ethanol succeeds readily with either (+)- or (-)-BTA (see Note d) to afford the R-isomer (23) or its S-enantiomer (24) in excellent optical yield.

Fig. 10



(20) (21)

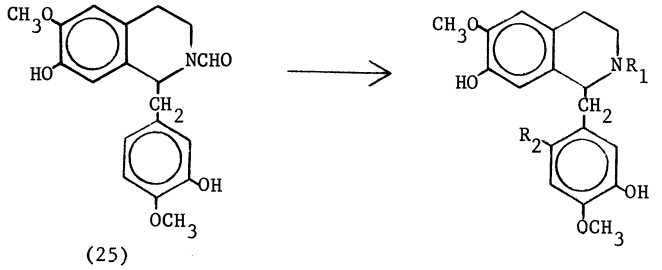
(23) R = ◄H (R-conf.)

(24) R = ---H (S-conf.)

(22)

Chemical modification of (22) affords a variety of important N-norreticuline derivatives all of which were obtained in crystalline form. These reactions, shown in Fig. 11, include N-formylation of (22) to give (25), which is easily convertible into racemic reticuline (26) by reduction with diborane. The preparation of 6'-bromo-derivatives can be accomplished by direct bromination of (25) in acetic acid to afford (27). N-Deformylation of (27) with hydrogen chloride in methanol affords the bromonorreticuline (28), and reduction with diborane yields bromoreticuline (29). These reactions can be equally well executed with optically active substances.

Fig. 11



(25)

(26) R_1=Me, R_2 = H

(27) R_1=CHO, R_2 = Br

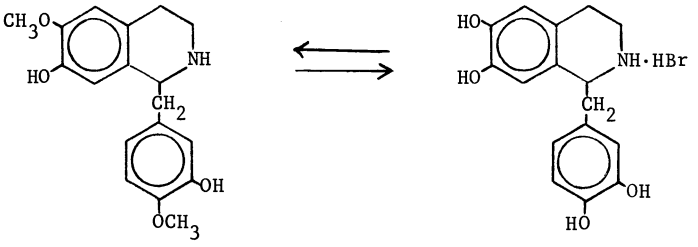
(28) R_1=H, R_2=Br

(29) R_1=Me, R_2=Br

Note d: (+)-BTA = (2R, 3R)-2'-bromotartranilic acid and its (-)-enantiomer (see Ref. 17) turned out to be uniquely suitable for the optical resolution of racemic N-norreticuline.

Direct conversion of (22) or its optical antipodes (23) or (24) into tetrahydropapaveroline (30 = THP) or its optical isomers hitherto prepared from N-norlaudanosine (Ref. 18), can now be readily accomplished by O-demethylation with boron tribromide (Ref. 19). THP is an important mammalian alkaloid (Ref. 2). Since catecholamines such as (30) can be partially O-methylated with catechol O-methyltransferases (Ref. 20), the relationship illustrated in Fig. 12 is of biochemical importance.

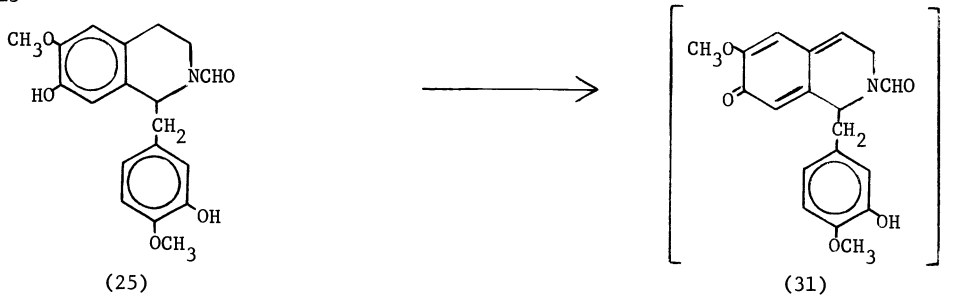
Fig. 12



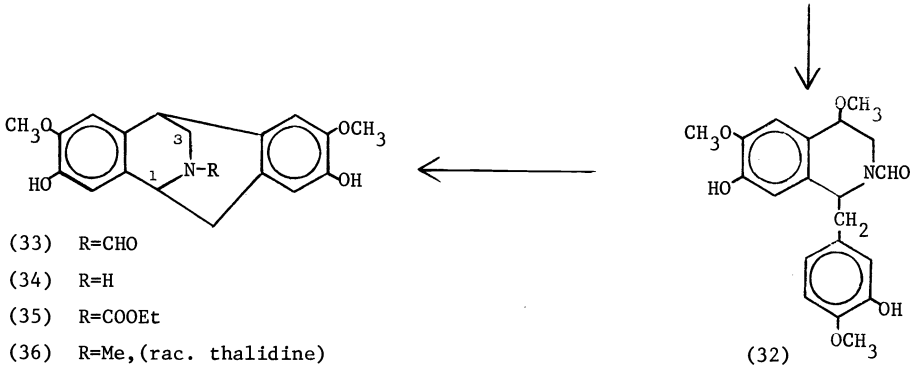
(22) (30)

The chemical potential of norreticuline in alkaloid synthesis is exemplified by a novel and facile conversion of its N-formyl derivative (25) into alkaloids belonging to the isopavinan group, as illustrated in Fig. 13.

Fig. 13



(25) (31)



(33) R=CHO
(34) R=H
(35) R=COOEt
(36) R=Me,(rac. thalidine)

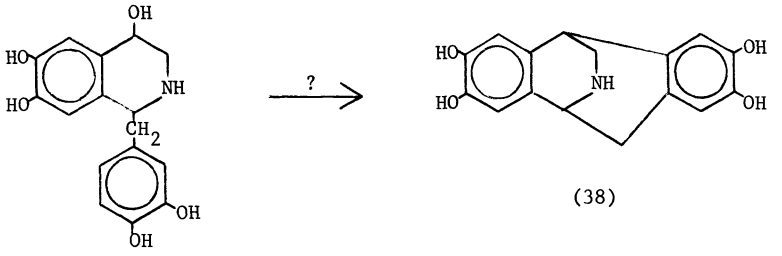
(32)

Chemical oxidation of (25) with DDQ in methanol at low temperature affords the intermediate quinone methide (31) which upon warming adds solvent to the reactive double bond to afford the 4-methoxy-tetrahydroisoquinoline (32). Oxidation of phenolic tetrahydroisoquinolines involving quinone methide intermediates may well be of biosynthetic significance. Compound (32) cyclizes readily with 1N hydrochloric acid to an isopavinan derivative (33). It is interesting to note that in this cyclization isomers belonging to the pavinan group of alkaloids (benzyl substituent bridges C-1 with C-3 in the tetrahydroisoquinoline moiety) could not be detected. This is in contrast to the conventional syntheses of these alkaloids starting with 1,2-dihydroisoquinolines (Ref. 21). The structure of the isopavinan system

present in (33) was proved by N-deformylation to racemic N-northalidine (34), conversion into its N-carbethoxy analog (35) and reduction with lithium aluminium hydride to the known racemic thalidine (36 (Ref. 22). The same sequences carried out with the optically active isomers (24) and (23) afforded natural (-)-thalidine (Ref. 23) and its "unnatural" (+)enantiomer.

Ether cleavage of racemic northalidine (34) with hydrobromic acid, shown in Fig. 14, affords the tetrahydroxy substituted isopavinan (38), a potential cyclization product of the hitherto unknown 4-hydroxy THP (37). The cyclization of 4-oxygenated derivatives of THP to isopavinanes and possibly pavinans under biological conditions is an interesting possibility.

Fig. 14

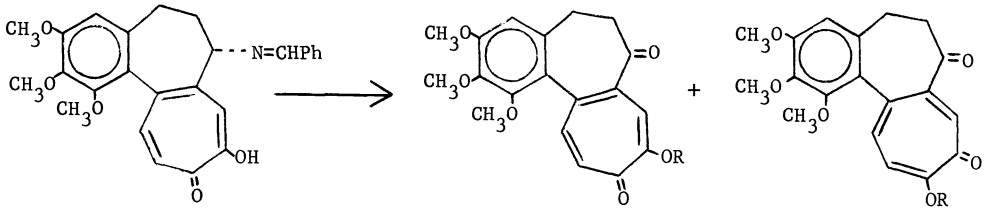


(37) (38)

CHEMICAL CONVERSIONS IN THE COLCHICINE SERIES

Repetition of Corrodi's synthesis of racemic colchicine by base catalyzed equilibration of the Schiff base (39) (Ref. 24) afforded in our hands a ketone as a major reaction product (Ref. 25). It was shown by single crystal X-ray analysis that this ketone exists as an almost equal mixture of the tautomers (40) and (41). They correspond in the arrangement of the oxygen functions in the tropolonic moiety to isocolchiceine and colchiceine, respectively, held together through hydrogen bonding. O-Methylation of the two enol ketones (40) and (41) afforded the corresponding O-methyl ethers (42) and (43), the latter probably identical to material obtained by a microbial degradation of colchicine (Ref. 26). The colchicine derivative (43), shown in Fig. 15, binds well to tubulin and therefore has potential antitumor activity (Ref. 27). Unnatural (+)-colchicine prepared in the course of this study turned out not to bind to tubulin, suggesting a rather interesting situation regarding substrate stereospecificity.

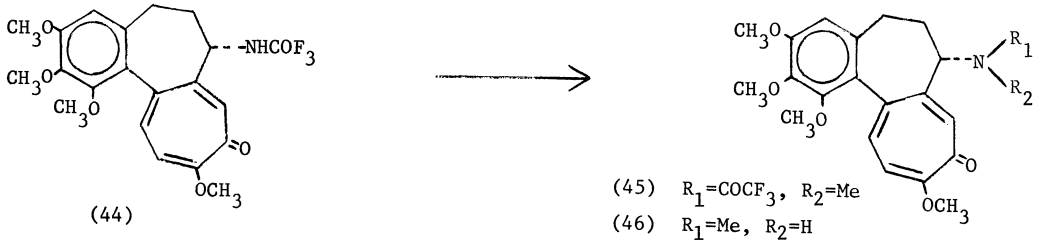
Fig. 15



(39) (40) (42) (41) (43)

Demecolcine (46), isolated as a minor alkaloid from Colchicum autumnale (Ref. 28) is an effective antineoplastic agent in chronic granulocytic leukemia (Ref. 29). An efficient synthesis of (46) from colchicine has been accomplished and is shown in Fig. 16.

Fig. 16



(44)

(45) R_1=$COCF_3$, R_2=Me

(46) R_1=Me, R_2=H

Treatment of deacetylcolchiceine with trifluoroaceticanhydride followed by methylation with diazomethane or methyl iodide and separation of the unnatural isomeric ether affords deacetyl-N-trifluoroacetyl colchicine (44). The proton on the nitrogen in (44) is much more acidic than the one present in colchicine and can be replaced by a methyl group to give N-trifluoroacetyl-demecolcine (45). Removal of the trifluoroacetyl groups in (45) under mild conditions affords chemically and optically pure natural demecolcine (46) in excellent yield. It is interesting that, in the end, our venture into the field of "unnatural alkaloids" indicated that they were needed for the synthesis of "real" alkaloids, demonstrating that in essence, the two cannot be separated from each other and belong to the same discipline called Natural Products Chemistry.

ACKNOWLEDGEMENT

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